

# **FDA Executive Summary**

## **Classification of Blood Establishment Computer Software (BECS) and BECS Accessories**

Prepared for the  
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Blood Products Advisory Committee

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# **1. Introduction**

The Food and Drug Administration (FDA) is convening the Blood Products Advisory Committee (BPAC) as a Device Classification Panel (the Panel) to discuss classification of blood establishment computer software (BECS) and BECS accessories.

The Panel will be asked to provide recommendations on the classification of BECS and BECS accessories as Class I, II or III medical devices based on the level of control necessary to provide a reasonable assurance of their safety and effectiveness.

If the Panel recommends Class II classification for BECS and BECS accessories, the Panel will also be asked to discuss special controls that would be sufficient to provide reasonable assurances of their safety and effectiveness. Special controls are regulatory requirements for class II devices. They are usually device specific and may include performance standards, postmarket surveillance, special labeling requirements, premarket data requirements, or other controls.

## **1.1. Current Regulatory Pathway for BECS and BECS Accessories**

The Federal Food, Drug, and Cosmetic Act (FD&C Act), section 513, established the risk-based device classification system for medical devices. BECS and BECS accessories have not been classified under this statutory provision. Currently these devices are regulated as unclassified devices, subject to 510(k) premarket notification requirements.

The 510(k) premarket notification is a submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective as (i.e., substantially equivalent to) a legally marketed Class I or II device of that same generic type. When determined to be substantially equivalent, the subject device may be legally marketed in the United States (U.S.).

The legally marketed device to which substantial equivalence is determined is known as the predicate device. A predicate device can be a preamendments device (legally marketed prior to the May 28, 1976 Medical Device Amendments to the FD&C Act) or a postamendments device that is, or was, legally marketed in the U.S. following the device amendments. A claim of substantial equivalence (SE) does not mean the new device must be identical to the predicate device. Substantial equivalence is based on a comparative assessment with respect to: intended use, design, energy used or delivered, materials, performance, safety, effectiveness, labeling, biocompatibility, standards, and other applicable characteristics that would demonstrate the device is as safe and effective as the predicate device.

Since the device amendments of May 28, 1976, BECS and BECS accessories have been found substantially equivalent to a device that was legally marketed prior to May 28, 1976 (preamendments device). The preamendments devices include Advanced Medical Systems, a computer based Blood Bank Management System used to perform compatibility testing and the American National Red Cross (ANRC) computer based Donor Deferral Register (DDR) used to determine temporary or permanent disqualification of donors.

## **1.2. Background on Device Classification**

### *Role of the Device Classification Panel*

The purpose of the Device Classification Panel is for the Panel to discuss and recommend the most appropriate classification for BECS and BECS accessories as Class I, II, or III devices.

Section 513(a) of the FD&C Act (21 U.S.C. 360c (a)) establishes three classes of devices based on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness: class I (general controls), class II (special controls in addition to general controls), and class III (premarket approval in addition to general controls).

Pursuant to section 513(d) of the FD&C Act (21 U.S.C. 360c (d)), FDA promulgates classification regulations classifying devices by generic type. A "generic type of device" is "a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness" (21 CFR 860.3(i)). FDA has issued regulations classifying the vast majority of preamendments devices (devices that were in commercial distribution before May 28, 1976) by generic type of device (See 21 CFR 860.84). Each classification regulation, located in 21 CFR parts 862-892, indicates the class (I, II, or III) in which FDA has classified the device type.

BECS and BECS accessories are unclassified devices. The Panel will be asked to recommend a classification for BECS and BECS accessories, after which FDA will propose a regulation that identifies and classifies this generic device type. Once finalized, this regulation will be published in the CFR.

### *Device Regulatory Controls*

All classes of medical devices are subject to general controls. General controls are the basic provisions (authorities) of the May 28, 1976 Medical Device Amendments to the FD&C Act, that provide the FDA with the means of regulating devices to ensure their safety and effectiveness. General controls in the FD&C Act apply to all medical devices. They include provisions that relate to adulteration; misbranding; device registration and listing; premarket notification; banned devices; including repair, replacement, or refund; records and reports; restricted devices; and good manufacturing practices.

Class I devices are subject to general controls and are typically exempt from submission of a premarket 510(k) notification. They generally pose the lowest risk to the patient and/or user.

Class II devices are subject to special controls in addition to the general controls provision of the Act. Special controls may include compliance with a recognized standard, warnings statements in the instructions for use, specific performance requirements, and/or other controls necessary to ensure a reasonable assurance of safety and effectiveness. Class II devices typically require FDA clearance of a premarket 510(k) notification to permit the device to be marketed and sold in the U.S.

Class III devices tend to present higher risk and they may be first-of-a-kind devices where general and special controls are not adequate to ensure their safety and effectiveness. Class III devices require FDA approval in the form of a premarket approval (PMA) application prior to marketing in addition to compliance with device general controls.

### *Device classification*

In order for FDA to classify BECS and BECS accessories per FD&C Act 513, the FDA proceeds through the following steps:

#### **STEP 1:**

FDA collects and reviews available information to identify valid scientific evidence relevant to the safety and effectiveness of BECS and BECS accessories, and weighs the probable benefit of BECS and BECS accessories in accordance with their intended use against the probable risks.

#### **STEP 2:**

FDA convenes a public meeting of the BPAC's Device Classification Panel to request the Panel's overall assessment of valid scientific evidence pertaining to the probable benefit

versus the probable risk of BECS and BECS accessories, and to obtain the Panel's recommendation on the classification of BECS and BECS accessories.

The meeting of the Panel provides an opportunity for members of the public, including medical device manufacturers, to present information to the panel during the public hearing portion of the meeting.

The Panel's recommendation for a proposed class for BECS and BECS accessories takes into account the regulatory controls necessary to provide reasonable assurance of the safety and effectiveness of BECS and BECS accessories for their intended use.

**STEP 3:**

After receipt of a classification recommendation from the Panel, FDA publishes a proposed classification regulation in the Federal Register for BECS and BECS accessories and provides interested persons an opportunity to submit comments on the proposed regulation.

**STEP 4:**

FDA reviews and considers all comments submitted by the public on the proposed regulation.

**STEP 5:** After review and consideration of all comments, FDA publishes a final regulation in the Federal Register classifying BECS and BECS accessories into Class I, II or III. The class, and any special controls if applicable, will establish which regulatory controls apply to this device type.

### **1.3. Device Description**

BECS and BECS accessories are devices used in the manufacture of blood and blood components to assist in the prevention of disease in humans by:

- identifying unsuitable donors;
- preventing the release of unsuitable blood and blood components for transfusion or for further manufacturing into products for human treatment or diagnosis;
- performing compatibility testing between the donor and recipient; and/or
- performing positive identification of patient and blood component.

A BECS accessory expands or modifies the function of the BECS and/or indications for use of the BECS device. These devices are intended for use with or capable of functioning with BECS for the purpose of augmenting or supplementing the BECS performance.

BECS and BECS accessories assist in the prevention of disease by performing functions for transfusion and donor management including the following:

- a. Manage issuance of blood components, inventory and tracking that can be used for lookback. Lookback is the process of tracing, identifying and notifying of recipients of blood components from donors who now test positive for certain infectious diseases.
- b. Determine compatibility between donor and recipient through the use of electronic crossmatch.
- c. Perform blood component release decisions.
- d. Establish positive patient identification at the bedside prior to transfusion by verifying that there is a correct match between the patient and the blood component.
- e. Evaluate, determine, and track donor screening information and component history such as:
  - Donor medical evaluation –history, physical exam
  - Donor suitability according to the health history questionnaire, e.g., donation frequency
  - Donor deferral
  - Testing results

### **1.3.1. Components for Operation of BECS**

BECS and BECS accessories may require non-BECS articles to operate, including:

- a. Other software, e.g., operating system
- b. Hardware, e.g., desktop or laptop computer, personal digital assistant (PDA) such as smart phone or tablet
- c. Peripherals, e.g., report printer, label printer, barcode scanner, monitor, keyboard, mouse, speakers

The focus of this Panel meeting does not include these articles.

### **1.3.2. Devices That Are Not BECS and BECS Accessories**

Medical Device Data Systems (MDDS), regulated under Section 880.6310, are Class I medical devices exempt from 510(k) premarket notification, and are not included for consideration under the BECS and BECS accessories classification.

21 CFR PART 880 -- GENERAL HOSPITAL AND PERSONAL USE  
DEVICES

Subpart G--General Hospital and Personal Use Miscellaneous Devices

## Sec. 880.6310 Medical device data system.

(a) *Identification.* (1) A medical device data system (MDDS) is a device that is intended to provide one or more of the following uses, without controlling or altering the functions or parameters of any connected medical devices:

- (i) The electronic transfer of medical device data;
- (ii) The electronic storage of medical device data;
- (iii) The electronic conversion of medical device data from one format to another format in accordance with a preset specification; or
- (iv) The electronic display of medical device data.

(2) An MDDS may include software, electronic or electrical hardware such as a physical communications medium (including wireless hardware), modems, interfaces, and a communications protocol. This identification does not include devices intended to be used in connection with active patient monitoring.

(b) *Classification.* Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter, subject to the limitations in 880.9.

These medical devices should not be confused with the medical devices described above in Section 1.3 as BECS and BECS accessories. A BECS accessory is distinct from MDDS because it expands or modifies the function of the BECS and/or indications for use of the BECS device. These devices are intended for use with or capable of functioning with BECS for the purpose of augmenting or supplementing the BECS performance.

## 2. Regulatory History of BECS and BECS Accessories

In the early 1980s, computer software grew to play a more important role in treating patients and preventing disease. In the mid-1980s, FDA formulated a strategy for regulating software, including software that is used in blood establishments, that was intended to protect the public health without stifling innovation. In 1987, the agency made available for comment a draft policy statement (Federal Register, Volume 52, Page 36104, September 25, 1987), which was revised and reissued in draft in 1989 as the "FDA Policy for the Regulation of Computer Products 11/13/89 Draft".<sup>1</sup>

In the 1989 Draft Policy, the agency stated its regulatory intentions regarding software products that meet the definition of medical devices, 21 U.S.C. § 321(h), and are not components, parts, or accessories of other articles which are themselves medical devices. FDA specified that such products would be subject to regulation as medical devices. Depending on its characteristics, a software device would be subject to one of several levels of regulatory control. FDA also stated that it would grant future exemptions from registration, listing, premarket notification, medical

device reporting and current good manufacturing practice (cGMP) requirements for certain products. However, any such exemptions would not apply to "manufacturers of computer hardware and software devices intended for use in blood banks."

With regard to software devices intended for use in blood establishments, FDA initially focused regulation of BECS at the user end, not at the software development stage. FDA provided guidance to blood establishments to help improve current Good Manufacturing Practices with regard to use and validation of software. FDA's Center for Biologics Evaluation and Research (CBER) issued memoranda in 1988<sup>2</sup> and 1989<sup>3</sup> to blood establishments regarding cGMPs applicable to computer software. The document stated that while such software is a device subject to device cGMPs, it is also regarded as equipment used in a blood establishment. Therefore, it is subject to blood and drug cGMPs under the Public Health Service Act, 42 U.S.C. § 201 et seq., and the Federal Food, Drug, and Cosmetic Act. The 1988 and 1989 CBER memoranda were directed to manufacturers of blood and blood products, and were intended to provide general guidance to blood establishments with regard to procedures for ensuring the security and confidentiality of data, and for system documentation.

In the early 1990s, however, a number of circumstances led FDA to determine that a regulatory approach that focused only on the user end was inadequate to assure the quality of software used in blood establishments and to protect the public health. During establishment inspections, FDA investigators observed numerous problems with software, including programs that posed significant risks to the public health, such as the potential for release of blood components found to be reactive when tested with assays for the Human immunodeficiency virus (HIV). Indeed, these observations revealed that unsuitable blood and blood components had been released and distributed as a result of improperly designed software. These observations resulted in warning letters and recalls of the unsuitable blood and blood components, as well as warning letters and recalls of the defective software. Furthermore, as blood establishment software programs became increasingly complex, FDA investigators found that validation at the user end was proving impracticable, and was insufficient to assure software performance. In addition, the then-chairman of the House Subcommittee with oversight responsibilities over FDA called for increased regulation of software products used for medical purposes.<sup>4</sup> Industry representatives also called for increased regulation, agreeing that such software should be regulated as a device, although they opposed premarket submission requirements.<sup>5</sup> In response to these circumstances, and after consideration of views expressed within the agency and by others, including industry representatives and congressional representatives, FDA determined that premarket submission pursuant to section 510(k) of the Act, 21 U.S.C. § 360(k) ("510(k) notifications"), were required for such software. CBER has been regulating BECS through the review of 510(k) premarket notifications and other premarketing and postmarketing regulatory controls of the Act since August 1996. In 1998, FDA sought recommendations from BPAC regarding the formal classification of BECS used as donor systems and transfusion management systems. BPAC

recommended regulating BECS as a Class II device. The formal classification of BECS was not finalized following this BPAC meeting. Consequently, the classification of BECS and BECS accessories is being newly presented for consideration at the December 3, 2014 Device Classification Panel of BPAC.

In 2002, FDA issued, “General Principles of Software Validation - Final Guidance for Industry and FDA Staff,”<sup>6</sup> that outlined general validation principles that FDA considers to be applicable to the validation of medical device software. Subsequently, in 2005, FDA issued “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”<sup>7</sup> to provide information to industry regarding the documentation that FDA recommends for inclusion in premarket submissions for software devices, including stand-alone software applications and hardware-based devices that incorporate software.

In recent years, CBER has conducted and participated in public meetings and workshops<sup>8,9</sup> on the elements BECS manufacturers should address in their 510(k) premarket notifications.

## **2.1.Previously cleared devices**

The first BECS 510(k) premarket notification was cleared by FDA on August 26, 1996. Information Data Management, Inc. submitted premarket notifications for their Components and Distribution Information System and Donor Management Information Systems. These devices were compared to systems marketed prior to the 1976 medical device amendments including the Blood Inventory Management System by Computer Sciences Corporation and the DDR developed by ANRC. Since 1996, FDA has cleared 204 BECS and BECS accessories under the 510(k) program.

Over the years, there have been a number of technology advances in BECS and their accessories including:

- a. Biometric donor identification (e.g., donor finger print identification)
- b. Computer aided donor self-administered health history questionnaire
- c. Computer-assisted analysis of donor unit and recipient sample test data for electronic crossmatch of blood units for transfusion
- d. Software controlled, remote release of blood units or components
- e. Remote or bedside positive patient identification (e.g., wireless handheld device with a barcode reader used to compare and match the blood product label and patient armband prior to transfusion)
- f. Wireless capability to receive donor and transfusion information

## **2.2. Cleared indications for use**

The indications for use (IFU) of a medical device, in general, is a description of the disease or condition the device will diagnose, treat, prevent, cure or mitigate and a description of the patient population for which the device is intended.

Over the past decades, indications for use for BECS and BECS accessories have varied in their complexity and content. These IFUs often stated a wide range of BECS/BECS accessory functions, including non-medical device functions. In general, the indications for use that represented medical device functions consisted of wording that demonstrated the device was indicated to aid in the prevention of disease by either identifying unsuitable donors or blood components, or in preventing the release of unsuitable or incompatible blood or components for transfusion to patients.

## **3. Literature Survey on BECS and BECS accessories**

FDA conducted a literature review of the safety and effectiveness of BECS and BECS accessories, to identify valid scientific evidence related to benefits and risks of these medical devices.

### **3.1. Methods**

A literature review was conducted through PubMed from August 11, 2014 through September 24, 2014 using the following search strings:

[electronic crossmatch for blood bank] OR [blood transfusion management system for blood bank AND software] OR [(donor suitability OR donor eligibility) AND software] OR (blood donor history questionnaire AND (computer OR software OR electronic)) OR ["transfusion management system" AND (computer OR software OR electronic)] OR [blood bank software AND blood establishments] OR [positive patient identification AND transfusion AND (computer OR software OR electronic)] OR [regulation of blood bank software].

The search included seven individual searches that are included in the string above. The initial search yielded 98 results. Titles and abstracts were reviewed for studies involving BECS and BECS accessories as well as features of BECS and BECS accessories. A total of 73 articles were excluded during the initial screening. Forty-seven were not relevant (e.g., general articles that address aspects of blood banking that do not address software), 10 were not specific to BECS, 9 were not in English, 2 were duplicates, 2 were for

manual methods, (e.g., general articles addressing blood banking but using paper methodologies) and 3 were not peer reviewed.

The full text of the remaining 25 articles was examined by two independent reviewers for inclusion in the literature review. Four articles were excluded from consideration because they did not contain safety and effectiveness information. A total of 21 articles were therefore retained for the literature review. Additional information regarding the methodology for inclusion and exclusion criteria is in Appendix A.

### **3.2. Results**

The review summarized below reflects the review of 21 articles which included 18 articles on transfusion management systems (positive patient identification and unit identification), electronic crossmatch and electronic release, and three articles on donor health history questionnaire used in donor management systems.

### **3.3. Literature Review**

No single publication comprehensively addressed the safety and effectiveness of BECS and all its functions. However, a number of articles assessed the safety and effectiveness of key functions of BECS transfusion management and donor management systems. These publications addressed 510(k) cleared and non 510(k) cleared BECS and BECS accessories. The articles originated in a number of countries, including Australia, China, Japan, Turkey, United Kingdom and the U.S.

The following summaries represent current information on the safety and effectiveness of BECS and BECS accessories as compiled from the published literature.

#### **3.3.1. Transfusion Management Systems**

It is recognized in the literature that human error, leading to the transfusion of an unsuitable or incompatible unit to a transfusion recipient, is among the most serious problems in transfusion therapy. Automating critical processes has been identified as one way to decrease the human error rate. These automated systems often consist of a personal digital assistant (PDA) with a barcode reader and are integrated with a stand-alone blood bank system or a blood bank module in a laboratory or hospital information system.

Linden et al.<sup>1</sup> reported on the transfusion errors in New York State. A 10 year study, between 1990 and 1999, showed 56% of transfusion associated errors were due to non-blood bank errors, e.g., identification error, phlebotomy error, incorrect order sent and

others. Of the 56%, 38% were due to identification errors. They reported that the single most frequent error was the administration of properly labeled blood to a recipient other than the one intended. The authors estimated that 1 in 12,000 blood transfusions was given to the wrong patient. They concluded that automation throughout the transfusion system may lessen adverse events attributable to human error.

Miyata et al.<sup>2</sup> reported that the survey performed by the Japanese Society of Blood Transfusion showed that 115 of 575 hospitals experienced at least one ABO blood type mismatched transfusion over a 5-year period. The major causes of transfusion errors were incorrect blood typing (15%) and failure to accurately identify blood component (42.8%) or recipient (11.5%). Transfusion errors were mainly caused by nurses and doctors at the bedside. The authors conducted a study to evaluate the efficacy of the network computer assisted transfusion management system to prevent human errors by monitoring the transfusion process. Over a three year period, more than 60,000 blood components were transfused without any ABO-mismatched transfusions. The authors concluded that the network computer assisted management system greatly contributed to safe and efficient transfusion therapy.

The functionalities for transfusion management systems include systems that positively identify the patient and blood components prior to transfusion, electronic crossmatch, and automated release of blood components.

#### **3.3.1.1. Positive Identification of Patient and Blood Components Using Barcode Technology**

Two studies reported the use of Immucor's I-TRAC Plus system. This is a point-of-care barcode transfusion safety system that links the patient's barcoded wristband with barcoded labels on blood sample tubes, blood component bags, and nurses' identification badges.<sup>3,4</sup> One study showed 100% positive identification for patients, their blood samples and blood components for transfusions.<sup>4</sup> The other study showed that the system prevented 12 cases of patient misidentification in a five year period. One of the 12 potential misidentifications occurred at the bedside.<sup>3</sup>

Ohsaka et al.<sup>5</sup> stated that The British Committee for Standards in Hematology recommended the use of information technology to prevent errors in the clinical transfusion process and in particular the use of barcode labeling of patient identification (ID) wristbands to enable patient ID by hand held scanners. Their study using a computer assisted transfusion management system showed that approximately 50,000 blood components were transfused over a 4.5 year period without a single mistransfusion (the wrong blood transfused to the patient).

Askeland et al.<sup>6</sup> studied a standalone barcode based transfusion system that consisted of four modules: blood sample collection, blood sample arrival in blood bank, dispensation from blood bank and product administration. They noted that a two-witness, two signature predecessor process is prone to error and that use of a barcode system could lessen the possibility of an adverse event. The data from their study demonstrated that, over a 46 month period after a barcode system was implemented, sample rejection rate due to clerical errors fell from 1.82 to 0.17% and incidence reports fell by 83%. Identification errors were being detected and prevented every 42.4 days. The authors estimated that the barcode base tracking system is 10 times safer than the manual method previously employed.

Ohsaka et al.<sup>7</sup> performed a study that demonstrated the effectiveness of a barcode based identification system for the patient and the blood component management. After the barcode system was in place, 5,627 autologous units were transfused over a 5.5 year period without a single mistransfusion.

Miller et al.<sup>8</sup> performed a study using the Blood Track system, patient safety software, and a 2D barcode. Only the bedside checking and administration components of the Blood Track system were utilized. This system prompted the user through each step of the blood checking process. The study concluded that 2D barcode technology and patient safety software significantly improve the bedside check of patient and blood product identification in an Australian setting. The pre-implementation transfusion audits demonstrated that only 76% transfusion episodes were checked correctly at the patient's bedside compared with 100% following introduction of barcode technology.

Anders et al.<sup>9</sup> revealed that usability is integral to the effectiveness of two barcode scanning devices. Their study indicated that a "user-needs" analysis as well as a comprehensive hazard analysis is necessary to ensure an effective design. Similarly, Miyata et al.<sup>2</sup> emphasized that decreasing errors requires the continuous redesign and implementation of safe systems.

Yenicesu et al.<sup>10</sup> piloted BT-online, a computer assisted transfusion system that uses barcode technology to prevent errors. This system includes audible warnings that are not only limited to product-patient mismatch but also alerts the user to critical steps. The software allows multiple procedures through a single terminal. This allowed the staff to recognize transfusion complications in a timely manner so that they could initiate appropriate treatment.

Sharma et al.<sup>11</sup> reported that most transfusion barcode positive identification studies have demonstrated incremental improvements in patient safety. However, a defect rate of around 2-3% has been demonstrated in large institutions due to failure points including noncompliance by the operator, device malfunctions and wristband print errors.

Shabestari et al.<sup>12</sup> evaluated alert-based monitoring (notification mechanisms to inform system managers of any errors) in blood transfusion management systems. They reported that, in most cases, an electronic system is more suitable for managing alerts. In their evaluation, only 29% of the alerts identified by the electronic system were identified by a manual monitoring process.

### **3.3.1.2 Positive Identification of Patient and Blood Components Using Radio Frequency (RF) Technology**

As noted above, barcode technology has been reported to reduce mistransfusion and to improve patient safety. Radio frequency (RF) technology has also been reported to do the same. Sandler et al.<sup>13</sup> evaluated a transfusion management system using a RF transponder microchip to standardize and document key steps in blood collection and transfusion process. The results of the study reported that multi-write, passive RF microchips can be used to standardize and document blood collections and transfusions, thereby reducing the potential for mistransfusion and improving patient safety.

### **3.3.1.3 Electronic Crossmatch and Remote Release**

Other functions of BECS transfusion management systems include electronic crossmatch and remote blood release. The ability to select and retrieve units or components from a blood refrigerator is controlled by the BECS. Four articles addressed these functions.

Cox et al.<sup>14</sup> developed a blood-issuing program in Australia where the selection of the compatible RBC units occurs outside the laboratory and the release of blood is performed by non-laboratory staffers utilizing a software driven protocol. It required extensive system validation and verification. This system allows remote site “self-serve” computer crossmatching. The study found that electronic remote blood release software provided a safe and efficient means of providing red blood cells within the blood bank and at remote hospitals without blood bank services.

Murphy et al.<sup>15</sup> described a 10 year project to implement an electronic transfusion service. This study along with the study conducted by Wong et al.<sup>16</sup> reemphasized that electronic release blood issue software reduced the time to make blood available for surgical patients and improved the efficiency of safe hospital transfusions.

Staves et al.<sup>17</sup> studied SafeTx and BloodTrack Courier for electronic remote blood release. SafeTx tracks blood bank products from receipt at the remote storage location to final disposition. BloodTrack Courier secures, tracks and verifies the movement of any blood product in and out of the remote storage location. The study found that of 5,200 RBC units, no units were incorrectly issued.

Murphy et al.<sup>18</sup> studied the functionality of the Haemonetics' BloodTrack electronic transfusion management system in monitoring transfusion practices. They reported that the software device has significant potential to increase the safety of blood transfusion, but that comprehensive education, training and continued support were needed.

### **3.3.2 Donor Management System**

Zuck et al.<sup>19</sup> addressed the computer assisted donor health history questionnaire as a BECS donor management system. They studied the use of Hoxworth Quality Donor System, a donor computer assisted audiovisual health history self-interview. The authors concluded that self-administered donor health history interview systems improve the safety of the blood supply.

Katz et al.<sup>20</sup> performed a study using the Quality Donor System (QDS), an audiovisual touch-screen computer-assisted self-interview (AVT-CASI), in which 50,000 donors were interviewed. The study compared the results from the QDS with face-to-face interviewing. The results showed that there was a decline of 61 percent in the rate of occurrence of errors and omissions resulting from use of the AVT-CASI and the identification of high-risk behaviors among first-time donors was 9 times greater than the face-to-face rate. They concluded that a well-designed audiovisual touch-screen donor self-interviewing system is superior to face-to-face interviewing and most likely more effective than interviewing donors by having them fill out a paper questionnaire.

Sanchez et al.<sup>21</sup> conducted a survey on the perceptions of health history screening with a computer-assisted self-administered interview (CASI). Their data from a large and diverse sample of U.S. blood donors concluded that using CASI might foster disclosures of deferrable risk without discouraging most donors from donating.

### **3.4. Summary of Literature**

A review of relevant literature pertaining to BECS and BECS accessories indicates the following:

- The widespread adoption of BECS introduction of computer systems in U.S. blood establishments has resulted in a decline in adverse events related to errors in the management of blood products. This includes greater accuracy in donor and patient identification as well as accurate crossmatching and transfusion management. Residual errors persist but, in most cases, can be attributed to defects in process control and to human errors that remain imbedded in the process.
- Effective management of blood donations and transfusion processes is necessary to insure proper care of donors and patients. Blood establishment computer systems that manage these processes are complex devices. The failure or malfunction of these devices can adversely affect donors and/or patients. As such, it would appear that continued review of premarket notification [510(k)] submissions is necessary to demonstrate a reasonable assurance of safety and effectiveness.

## **4. Medical Device Reports (MDRs)**

### **4.1. Overview of MAUDE Database**

The Manufacturer and User Facility Device Experience (MAUDE) houses medical device reports (MDRs) submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. Mandatory and voluntary reporters submit medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products.

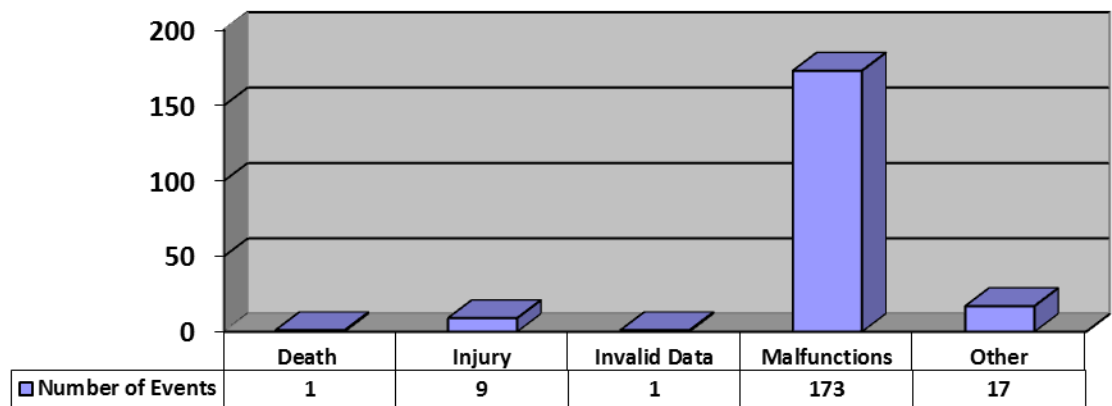
Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data.

### **4.2. MAUDE Search Results:**

FDA conducted queries of the MAUDE database from October 7, 2014 through October 17, 2014 to identify MDR reports related to the use of BECS and BECS accessories. The search was restricted to the period January 1, 1996 through October 17, 2014, and

utilized the device product code “MMH,” for standalone blood bank software. There were 201 events that included one death, nine injuries, one invalid event (incomplete information), 173 malfunctions and 17 “other” events reported over 19 years.

### MDR Event Types

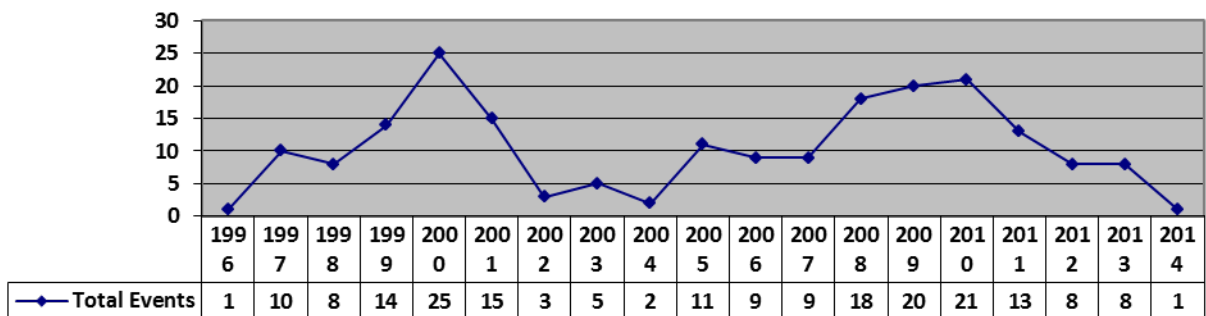


The patient death occurred in 2002 and was attributed to a mechanical failure of the blood refrigerator. The BECS was not implicated in the death of the blood recipient.

Nine injuries were reported over 19 years. The details of the reports are insufficient to accurately identify the nature of the injuries. One of the nine injuries reported indicated that hospitalization was required.

The total MDR events related to BECS and BECS accessories per year are listed below.

### Total MDRs per Year



One hundred and seventy-three malfunctions were reported between January 1, 1996 and October 17, 2014. The manufacturer evaluation of the malfunctions resulted in some malfunctions being classified in multiple categories. The categories include:

Software Problem (non-described)- 121  
Computer software problem (error/design)- 93  
Software Requirement Error- 6  
User Error- 12  
Other (e.g., labeling, operational problems)- 70

Examples of reported malfunctions include:

- a. Software requirements not clear, i.e., donor records inappropriately merged when a user edited the name of a donor on a certain screen.
- b. Software design failure, i.e., quarantine status applied by blood center staff is inadvertently overwritten when mobile donor collection data were synchronized from a thumb drive.
- c. Software design failure, i.e., allowing an electronic crossmatch without two verified ABO blood types by serology.
- d. Interface, i.e., when antibody screen interpretation results are sent via an instrument interface, reflex orders based on this interpretation are not triggering appropriate testing (failure to perform an antibody identification test subsequent to detection of a positive antibody screening test).

#### **4.3. Conclusion**

BECS malfunctions reported through MAUDE have the potential to cause death or serious injury. These medical device reports suggest that the current requirement for premarket notification [510(k)] review of BECS and BECS accessories is an effective means of minimize death or serious injury from software malfunctions.

## **5. BECS Recalls**

### **5.1. Recalls Overview**

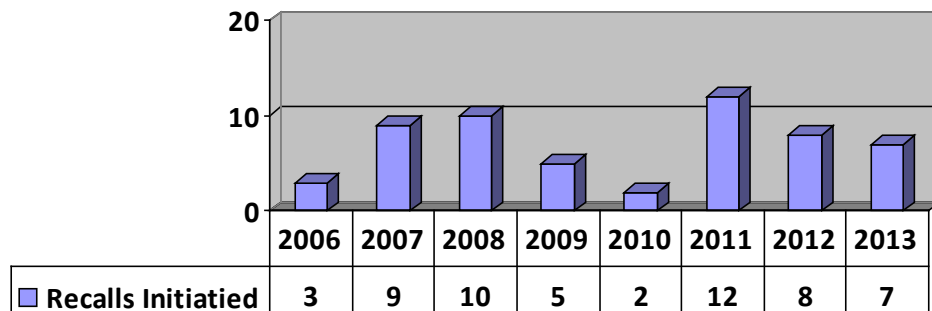
A recall is an action taken to address a problem with a marketed medical device that violates FDA law. Recalls occur when a medical device is defective, when it could be a risk to health, or when it is both defective and a risk to health. A medical device recall does not always mean that the user must stop using the product or return it to the company. A recall sometimes means that the medical device needs to be verified, adjusted, or fixed. A recall is either a correction or a removal depending on where the action takes place. Note that classification of a recall as Class I, II, or III is unrelated to the classification of medical devices.

Recalls are classified as follows:

- Class I: a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.
- Class II: a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequence is remote
- Class III: a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

From 2006 through 2013, there have been 56 recalls of BECS and BECS accessories. All of the deviations were classified as “product specifications not met” which included programming errors, inadequate design requirements and incorrect implementation of the design. See the summary table below for the BECS and BECS accessories recalls initiated from January 1, 2006 through December 31, 2013.

#### BECS and BECS Accessories Recalls Initiated Per Year



Examples of these recalls include:

- a. A programming loop error that allowed unwanted test results to be saved when the user selected “No” at the prompt “Save? Yes or No.”
- b. The software logic of a donor management system was not designed to handle an overdue review of required test data, causing the elimination of certain required questions from the donor history questionnaire. The donor was subsequently presented with the abbreviated donor questionnaire instead of the required full length questionnaire.

- c. A limitation in the character field for the antigen identification string resulted in the antigen results not being saved to the blood bank specimen or blood bank history records because the antigen identification string exceeded a certain number of characters.
- d. A new version of software containing a design error was released without performance of adequate validation to ensure that the deferral status was displayed to the screener. The design error could result in a failure to identify a donor as deferred.

## **5.2. Conclusion**

Fifty-one of the 56 recalls were classified as Class II recalls and 5 were classified as Class III recalls by FDA. There were no Class I recalls. These recalls suggest that the current requirement for premarket notification [510(k)] review of BECS and BECS accessories is an effective means to minimize death or serious injury from software malfunctions.

## **6. Development of Standards for Software in Medical Devices**

Software design presents some unique characteristics. BECS and BECS accessories share these characteristics and make up the challenge faced when identifying the appropriate regulatory controls in medical device classification. Some of the unique characteristics in software devices include the following.

- a. The majority of software device defects are traceable to errors made during the design and development process. Software device manufacturing consists of reproduction that can be easily verified. It is not difficult to manufacture thousands of software devices that function exactly the same as the original. The difficulty is in manufacturing an original software device that meets all specifications. One of the most significant features of software is branching, i.e., the ability to execute alternative series of commands based on differing inputs. This feature is tied to another characteristic of software - its complexity. Even short programs can be very complex.
- b. Typically, testing alone cannot fully verify that a software device is complete and correct. In addition to testing, other verification techniques and a structured and documented development process are needed to ensure a comprehensive validation approach.
- c. A software device is not a physical entity and does not wear out. In fact, a software device may improve with age, as latent defects are discovered and removed. However, since

software devices may be updated and changed regularly, such improvements are sometimes countered by new defects introduced into the software device during the change.

- d. Software device failures may occur without advanced warning. The branching or algorithms, which allow differing paths during execution, may hide latent defects until long after a software device has been introduced into the marketplace.
- e. Another related characteristic of a software device is the speed and ease with which it can be changed. This factor can cause both software and non-software professionals to believe that software problems can be easily corrected. This, combined with a lack of understanding of software, can lead manufacturers to believe that tightly controlled engineering is not needed for software devices, in the same way that it is for hardware. In fact, the opposite is true. Because of its complexity, the development process for software devices should be even more tightly controlled, in order to prevent problems that cannot be easily detected later in the development process. Therefore, accurate and thorough documentation of product development is essential.
- f. Seemingly insignificant changes in software code can create unexpected and very significant problems elsewhere in the software device. The development process for a software device should be sufficiently well planned, controlled, and documented to detect and correct unexpected results from software changes.

For these and other reasons, software engineering needs an even greater level of manufacturing scrutiny and control. Significant efforts have been applied to the development of standards to address these unique characteristics and to ensure the safety and effectiveness of software devices. Two standards form the foundation for the safety and quality of software: ISO IEC 62304 “Medical device software-Software life cycle processes” and ISO IEC 12207 “Systems and software engineering-Software life cycle processes.”

### **6.1. ISO IEC 62304 Medical device software-software life cycle processes**

This International standard, recognized by FDA, states that establishing the safety and effectiveness of a medical device containing software requires knowledge of what the software is intended to do and a demonstration that the use of the software fulfils those intentions without causing any unacceptable risks.

This standard provides a framework of life cycle processes with activities and tasks necessary for the safe design and maintenance of medical device software. This standard provides requirements for each life cycle process. Each life cycle process is further divided into a set of activities, with most activities further divided into a set of tasks. This

standard establishes a common framework for medical device software life cycle processes.

## **6.2. ISO IEC 12207 Systems and software engineering-Software life cycle processes**

This international standard officially replaced US Military Standard-498 (MIL-STD-498) for the development of Department of Defense software systems whose purpose was to establish uniform requirements for software development and documentation for the US military. The ISO IEC 12207 standard defines all the tasks required for developing and maintaining software. It establishes a common framework for software life cycle processes, with well-defined terminology, that can be referenced by the software industry. It applies to the acquisition of systems and software products and services, to the supply, development, operation, maintenance, and disposal of software products and the software portion of a system.

## **7. Risks to Health**

The risks to health associated with BECS and BECS accessories include, but are not limited to the following:

- a. Transfusion reaction or death from the inadvertent release and transfusion of incompatible blood or blood components
- b. Transfusion injury from the transfusion of inaccurately labeled and/or stored blood components,
- c. Transfusion injury or death from the release of blood components from otherwise ineligible donors. For example, the transmission of infectious diseases from the inadvertent release of blood components that have tested positive for transfusion-transmitted disease agents.
- d. Donor injury from inappropriate or excessive donation of blood or blood components.

***The panel will be asked to comment on the risks to health that have been identified by FDA, whether these risks have been correctly identified, and whether there are additional risks to health that should be considered for BECS and BECS accessories.***

## 8. Summary

Based on the available information, the panel will first be asked to comment on whether BECS and BECS accessories meet the statutory definition of a Class III medical device.

Under the law, a class III device is a device because:

- (i) it
  - (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and
  - (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and
- (ii)
  - (I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or
  - (II) presents a potential unreasonable risk of illness or injury, is to be subject, in accordance with section 360e of this title, to premarket approval to provide reasonable assurance of its safety and effectiveness.

If BECS and BECS accessories do not meet the statutory definition of a Class III device, the panel will be asked whether BECS/BECS accessories would more appropriately be classified as a Class II device. FDA classifies a device as class II for which general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. Special controls are usually device-specific.

If the panel decides that BECS/BECS accessories are neither class III or class II devices, the panel, therefore, believes that general controls alone are adequate to ensure a reasonable assurance of safety and effectiveness for BECS/BECS accessories and should be classified as a Class I medical device.

For the purposes of classification, the following items should also be considered as outlined in 21 CFR 860.7(b):

- (1) The persons for whose use the device is represented or intended;
- (2) The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other

- intended conditions of use;
- (3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
- (4) The reliability of the device.

### **8.1. Indications for Use**

BECS and BECS accessories are devices used in the manufacture of blood and blood components to assist in the prevention of disease in humans by:

- identifying unsuitable donors;
- preventing the release of unsuitable blood and blood components for transfusion or for further manufacturing into products for human treatment or diagnosis;
- performing compatibility testing between the donor and recipient; and/or
- performing positive identification of patients and blood components.

A BECS accessory expands or modifies the function of the BECS and/or indications for use of the BECS device. These devices are intended for use with or capable of functioning with BECS for the purpose of augmenting or supplementing the BECS performance.

### **8.2. Valid Scientific Evidence**

In making a recommendation regarding the safety and effectiveness of BECS and BECS accessories, the panel will be asked to consider “valid scientific evidence.” According to 21 CFR 860.7(c)(2), “Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.”

### **8.3. Reasonable Assurance of Safety**

According to 21 CFR 860.7(d)(1), “There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.”

A reasonable assurance of safety exists if, when using the device properly:

- a. The probable benefits to health outweigh the probable risks; and
- b. There is an absence of unreasonable risk of illness or injury.

### **8.4. Reasonable Assurance of Effectiveness**

According to 21 CFR 860.7(e)(1), “There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

## **9. FDA Summary and Recommendation**

### **9.1. Summary of Valid Scientific Evidence**

Based on the available information for BECS and BECS accessories, there is evidence that the benefits from use of this device type outweighs the potential risk. The literature indicates that computer assisted transfusion management systems and donor service systems improve the safety and effectiveness of transfusion and donor management. However, medical device reports and device recall data indicate that this device type presents risks, and that clear design requirements and extensive verification and validation are needed to ensure the safe and effective use of BECS and BECS accessories.

Due to the risk associated with BECS/BECS accessories, and the complexities of this device type, FDA proposes that general controls alone are not sufficient to ensure the safety and effectiveness of BECS and BECS accessories. FDA proposes that special

controls are required. Under the statute, a device is potentially class III if it is “life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health.” FDA believes that BECS and BECS accessories are not “life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health.

## 9.2. Special Controls

FDA believes that special controls, in addition to general controls, should be established to mitigate the risks to health identified below and provide a reasonable assurance of the safety and effectiveness of BECS and BECS accessories.

**Table 3: Risk/Mitigation Recommendations for BECS and BECS Accessories**

Identified Risk	Recommended Mitigation Measure
Transfusion reaction or death	<ul style="list-style-type: none"> <li>• performance and functional requirements</li> <li>• performance testing</li> <li>• labeling</li> </ul>
Transmission of infectious disease	<ul style="list-style-type: none"> <li>• performance and functional requirements</li> <li>• performance testing</li> <li>• labeling</li> </ul>
Donor health risk from too frequent or inappropriate donation	<ul style="list-style-type: none"> <li>• performance and functional requirements</li> <li>• performance testing</li> <li>• labeling</li> </ul>

FDA believes that BECS and BECS accessories should be subject to the following special controls:

- (1) Software performance and functional requirements are provided in the premarket submission including detailed design specifications, e.g., algorithms or control characteristics, alarms, device limitations, and safety requirements.
- (2) Verification and validation testing and hazard analysis are to be performed and provided in the premarket submission.
- (3) Labeling includes:
  - (i) Software limitations;
  - (ii) Unresolved anomalies, annotated with an explanation of the impact on safety or effectiveness;
  - (iii) Revision history; and,
  - (iv) Hardware and peripheral specifications.

- (4) Traceability Matrix performed and provided in the premarket submission.
- (5) Performance testing is performed and provided in the premarket submission, as necessary to ensure the safety and effectiveness of the system, and when adding new functional requirements, (e.g., electrical safety, electromagnetic compatibility, or wireless coexistence).

***If the panel believes that Class II is appropriate for BECS and BECS accessories, the panel will be asked whether the identified special controls appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.***

### **9.3. FDA Recommendation**

Based on the safety and effectiveness information outlined above, and the identified benefits and risks, FDA recommends the classification of BECS and BECS accessories as Class II devices subject to special controls. The following regulatory language is proposed:

#### **864.XXXX Blood establishment computer software and BECS accessories**

(a) Identification. Blood establishment computer software (BECS) and BECS accessories are devices used in the manufacture of blood and blood components to assist in the prevention of disease in humans by identifying unsuitable donors, preventing the release of unsuitable blood and blood components for transfusion or for further manufacturing into products for human treatment or diagnosis, performing compatibility testing between donor and recipient and performing positive identification of patients and blood components. A BECS accessory expands or modifies the function of the BECS and/or indications for use of the BECS device. These devices are intended for use with or capable of functioning with BECS for the purpose of augmenting or supplementing the BECS performance.

(b) Classification. Class II (special controls). The special controls for this device are:

- (1) Software performance and functional requirements are provided in the premarket submission including detailed design specifications, e.g., algorithms or control characteristics, alarms, device limitations, and safety requirements.
- (2) Verification and validation testing and hazard analysis are performed and provided in the premarket submission.
- (3) Labeling includes:
  - (i) Software limitations;

- (ii) Unresolved anomalies, annotated with an explanation of the impact on safety or effectiveness;
  - (iii) Revision history; and,
  - (iv) Hardware and peripheral specifications.
- (4) Traceability matrix is performed and submitted in the premarket submission.
- (5) Performance testing is performed and provided in the premarket submission, as necessary, to ensure the safety and effectiveness of the system, and when adding new functional requirements, (e.g., electrical safety, electromagnetic compatibility, or wireless coexistence).

***The panel will be asked for their recommendation on the appropriate classification of BECS and BECS accessories.***

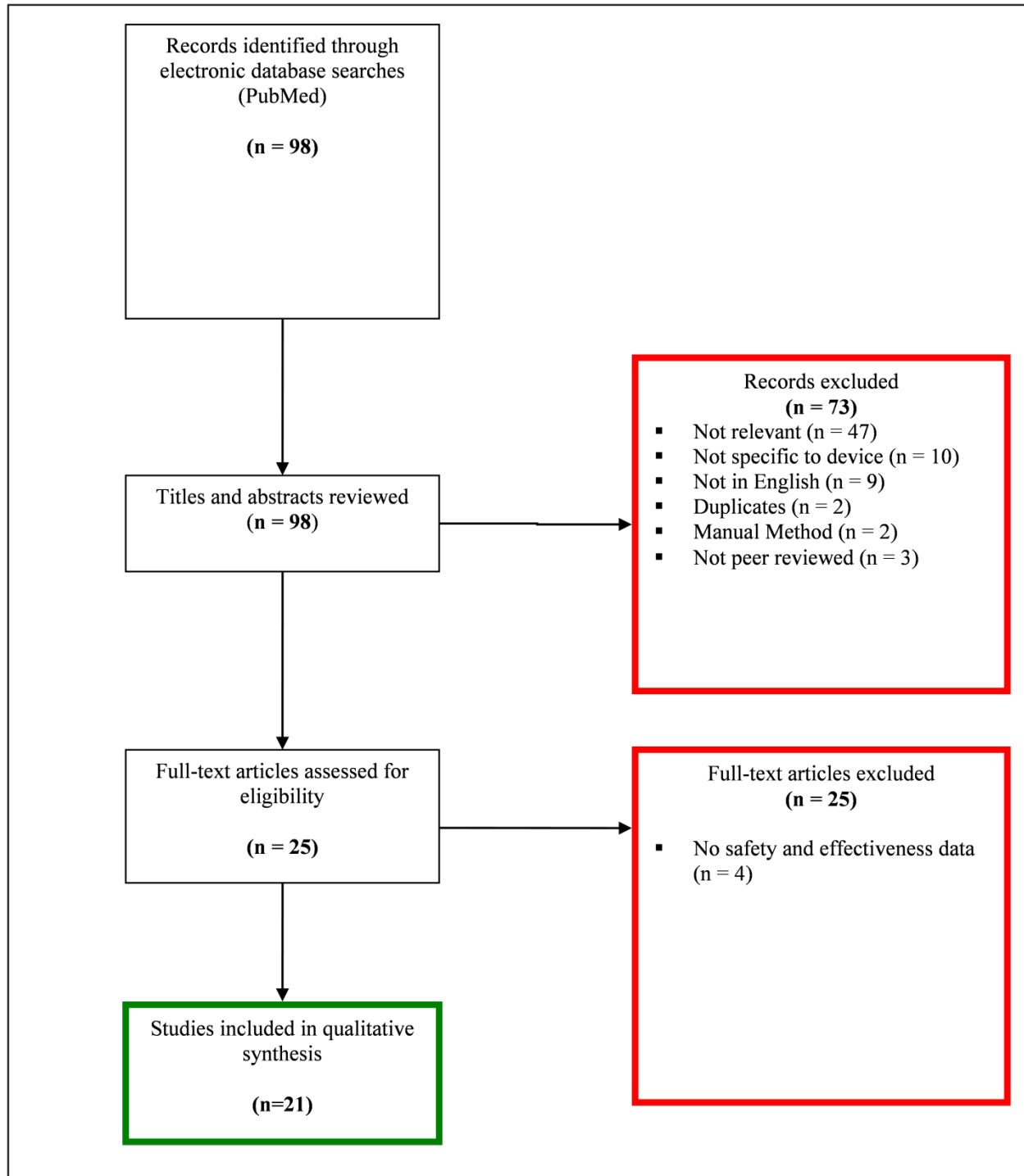
**Questions for the Device Classification Panel** -Questions are in a separate document.

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## Appendix A



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